CPCH0161523D

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The Specification

Ajimycin crystal and preparation method thereof

The present invention pertains to an ajimycin crystal and a preparation method thereof.

Ajimycin (chemical name: N-methyl-9a-aza-9-deoxo-9-dihydroerythromycin A) is derived from erythromycin A, and is a broadspectrum antibiotic. Compared with erythromycin, ajimycin has a broader antibiotic spectrum, has brilliant acidic stability, is suitable for oral administration and has perfect pharmacokinetic properties. The U.S. Patents US4,512,982. US4,518,590; US 4,328,334 and US 4,474,768, and US4,517,359 disclose methods for synthesizing ajimycin and the hydrates thereof: dissolving a methylated crude in hot ethanol; adding water gradually until the solution appears slightly turbid; standing the solution overnight, from which ajimycin is crystallized; then recrystallizing ajimycin in the same way. A disadvantage of this method is that the ajimycin hydrate obtained from said method is hygroscopic in air and is not easily preserved at a normal temperature, thus making the preparation production quite difficult. European Patent EP298650 discloses that the non-hygroscopic azithromycin in the form of a dihydrate crystal, which is prepared by crystallization of azithromycin using a mixture of tetrahydrofuran, an aliphatic C5-C7 hydrocarbon and water as the solvent. The disadvantages of this method are that the tetrahydrofuran and aliphatic C5-C7 hydrocarbon are very expensive, and that it is difficult to recover the solvent as the boiling point of tetrahydrofuran and that of the aliphatic C5-C7 hydrocarbon are slightly different.

An object of this invention is to make ajimycin less hygroscopic, to lower the cost for the crystallization of the ajimycin hydrate, to provide the ajimycin crystal with a better fluidity and the pharmaceutical preparation with a higher bioavailability, thus to obtain an ajimycin crystal and a preparation method thereof.

An object of this invention is to provide an ajimycin crystal having brilliant fluidity and a proper amount of non-crystal water. To be specific,

the ajimycin crystal in the present invention contains less than 4% of adsorption water, and has the following features:

1. The infrared spectrum (KBr) shows the frequencies of the following groups:

Wave number cm^{-1}	group
1000-1200	C-O-C
1340-1460	-CH2
1719	-C-O
1380	N-CH3
2780-3020	-CH3
3400-3600	-OH, H2O

There are characteristic absorption peaks at 3600-3400cm^{-1}, 3020-2780cm^{-1}, 1719cm^{-1}, 1460-1340cm^{-1}, 1380cm^{-1} and 1200-1000cm^{-1}.

2. Ultraviolet absorption spectrum:

The ajimycin crystal of the present invention has a maximum absorption wavelength λmax=207.7nm

3. Analysis on elements:

Theoretical values(%)	C60.93	H9.69	N3.74
Actually tested values(%)	C59.49	H9.87	N3.74

4. Analysis on heat differences:

Comparing the DSC curve of the sample with that of the imported control, one can see that the two curves are substantially the same, except that the melting heat of the sample is only a half of that of the imported control: 5.83 calories/t (sample) and 13.14 calories/gram (imported control). The comparison shows that the ajimycin (sample) of the present invention contains adsorption water.

5. Nuclear magnetic resonance spectrum (NMR)

a. H-NMR has the following features:

'H-NMR(CDCl2) δ is 2.28[3'-N(CH3)2], 2.34(9a-NCH3);

b. C-NMR has the following main features:

^{13}C-NMR(CDCl3) δ is 178.91(C-1), 78.14 and 83.32(C-3, C-5), 36.14(9a-NCH3), 40.34[3'-NC(CH3)2].

6. Thermogravimetric analysis (TGA)

As the temperature arises, the gravity of the sample reduces evenly from 50 to 105℃.

7. X-ray diffraction:

θ °	interplanar spacing d (A)	I/10	θ °	interplanar spacing d (A)	I/10
7.58	11.65	7	19.04	4.66	15
7.80	11.33	26	19.62	4.52	12
9.40	9.40	20	20.40	4.35	26
9.80	9.02	100	20.96	4.24	14
10.06	8.79	5	21.76	4.08	10
11.20	7.89	29	22.60	3.93	9
11.42	7.74	9	23.46	3.79	7
11.94	7.41	7	24.52	3.63	8
12.40	7.09	23	24.76	3.60	9
13.94	6.35	11	25.22	3.53	7
15.72	5.63	15	29.50	3.03	5
16.08	5.51	9	31.24	2.86	5
16.58	5.34	8	32.76	2.73	4
18.42	4.81	9	34.86	2.57	4
18.86	4.70	19	35.14	2.55	4

Another object of this invention is to provide a method for preparing said ajimycin crystal, which mainly comprises dissolving a water-contained

ajimycin in a mixture of a water-soluble organic solvent and water, crystallizing and drying it.

The detailed steps and technological conditions for said preparation method are as follows:

The relative weight ratio of the water-contained ajimicin:water:water-soluble organic solvent is 1: 30-1000: 9-16;

The water-soluble organic solvent is selected from the group consisting of ethanol, acetone, iso-propanol, propanol, 1,2-propylene glycol, 1,2-propylene glycol, propionitrile, 2-chlorohydrin, N,N,N',N'-tetramethylurea, N-methylpyrrolidone, allyl alcohol or a mixture thereof;

The organic solvent is preferably acetone, ethanol or a mixture thereof;

The drying is vacuum drying for 4 to 5 hours.

The present invention is further illustrated with the examples provided hereinafter:

The table below shows the experimental results concerning the stability of the ajimycin crystal of the present invention (at a temperature of 10-32 ℃, and a dampness of 25-80%):

Storage time (month)	Amount of water(%)
0	3.3
1	3.4
3	3.5
6	3.5
12	3.6
17	3.6

It can be seen from the above data that, sampling the ajimycin of the present invention after 0, 1, 3, 6, 12 and 17 month(s), one measures said

ajimycin and finds that the amount of water contained therein is 3 to 4%. An amount of less than 4% may satisfy the requirement of an industrial production.

With respect to the preparation of ajimycin crystal according to the examples:

(1) 100 grams of water-contained ajimycin prepared according to the U.S. patents US4517359 and US4474768 was dissolved at 50℃ in 400ml of acetone, to which water was added dropwise up to 600ml. The mixture was stirred slowly for five hours at a speed of 200 to 300 rotates/minute, cooled to an ambient temperature and filtered. It was then washed with 3 ×100ml of a mixture in which acetone:water=1:2, and vacuum dried at 40-50℃ for 4-5 hours (0.08MPa-0.09MPa) until 3.0-4.0% of water is left, to yield 86.1 grams of ajimycin crystal.

(2) 100 grams of water-contained ajimycin prepared according to the U.S. patents US4517359 and US4474768 was dissolved at 50℃ in a mixture of 400ml ethanol and 400ml of acetone, to which water was added dropwise up to 600ml. The mixture was stirred slowly for five hours at a speed of 200 to 300 rotates/minute, cooled to an ambient temperature and filtered. It was then washed with 3×100ml of a detergent liquid in which ethanol:acetone:water=1:1:4, and vacuum dried at 40-50℃ for 4-5 hours (0.08MPa-0.09MPa) until 3.0-4.0% of water is left, to yield 86.1g of ajimycin crystal.

Hereinafter are the substantive features and notable progress of the present invention:

The ajimycin crystal provided by the present invention is a stable compound. Compared with the dihydrate ajimycin crystal imported abroad, the ajimycin crystal of the present invention has brilliant fluidity and is suitable for preparing pharmaceutical preparations. In addition, since the ajimycin crystal of the present invention is a non-dihydrate crystallized-type Ajimycin, it has excellent bioavailability in pharmaceutical preparations. Moreover, the preparation method of this invention uses easily obtained reagent, and is convenient to operate.

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